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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,166	01/02/2003	Werner Mederski	MERCK 2033A	9705

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,166	MEDERSKI ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,4,7,9,15-21,29,30,40,41,47 and 48* is/are allowed.

6)☒ Claim(s) *3,5,6,10-14,22-27,31-33,35-39,42-46,49-55 and 59-73* is/are rejected.

7)☒ Claim(s) *28,34 and 56-58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of 01-29-04 has been fully considered. While the amended claims have overcome the previous rejections of 112/2nd and 101, they raise new ground(s) of rejections under 112/1st and 2nd paragraphs as well as 102. Also, new claims raise new ground(s) of rejections, and are still anticipated by the teachings of Bhaduri et. al. and Houghten et. al. Therefore, the previous 102 rejection is maintained herein along with new rejections under 112/1st, 2nd paragraphs and 102.

Claim 8 has been cancelled. The added set of claims has 2 'claim 48'. So, the second claim 48 is renumbered as claim 49. Therefore, pending claims are 1-7, and 9-73.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 5, 6, 12, 31, 32, 35, 38, 39, 42, 45, 46, 49, 55, 56, and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of thrombosis and peripheral circulatory disorders, does not reasonably provide enablement for the treatment of other diseases such as **myocardial infarct, arteriosclerosis, angina pectoris, acute coronary syndrome, stroke, transient ischemic attack, or reocclusion/restenosis after angioplasty/stent implantation**. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claims 5, 31, 38, 45, and 55 are drawn to "a method of antagonizing glycoprotein IbIX…", which encompasses the treatment of many disorders including thrombosis, peripheral circulatory disorder, myocardial infarct, arteriosclerosis, angina pectoris, acute coronary syndrome, stroke, transient ischemic attack, or reocclusion/restenosis after angioplasty/stent implantation. While many of the cardiovascular disorders are caused by the blockage of blood vessels, such a blockage is mostly formed by the deposit of cholesterol and platelets on the inside wall of the vessels. Thus, for a compound to antagonize glycoprotein IbIX, it does not mean that it could treat many of the complicated cardiovascular disorders such as those claimed herein.

The amount of direction or guidance presented: The specification does not appear to provide bioassays to test for the antagonistic effect of compounds claimed herein. Note, the specification does not provide *in-vitro* data to show which of those claimed compounds could actually antagonize glycoprotein IbIX. Thus, given a large genus claimed herein, the skilled chemist would have to carry out more than routine experimentation to determine which compound could antagonized glycoprotein IbIX. The specification also does not provide any correlation between glycoprotein IbIX to any of the disorders such as: myocardial infarct, arteriosclerosis, angina pectoris, acute coronary syndrome, stroke, transient ischemic attack, or reocclusion/restenosis after angioplasty/stent implantation.

The majority of those disorders (e.g., myocardial infarct, arteriosclerosis, angina pectoris, acute coronary syndrome, stroke, transient ischemic attack) is caused by the deposit of cholesterol and platelets aggregation in the blood vessels as well as stress. However, the specification does not show the relationship of glycoprotein IbIX with cholesterol or platelets. Thus, it could not be perceived how antagonizing glycoprotein IbIX could treat any of said disorders.

As for reocclusion/restenosis after angioplasty/stent implantation, said condition is the tissue formation or scarring when the stent is implanted or replaced. Such a condition is related more with cell growth around (or over) the stent. Thus, unless glycoprotein is shown to affect tissue growth, its role in treating reocclustion/restenosis is not evident from the mere treatment of thrombosis.

The state of the prior art: Typically, quinazolinone compounds are known for their antiviral or antibacterial activity, and not for cardiovascular activity. Furthermore, the commercially available drugs that treat thrombosis such as: Coumadin, Trental, etc., have not been used to treat myocardial infarct, arteriosclerosis, angina pectoris, acute coronary syndrome, stroke, or transient ischemic attack. Also, the antagonizing glycoprotein IbIX is not a well established pathway that would allow the skilled clinician to extend its application without knowing the risk.

Thus, with the limited teaching and **unpredictable nature** of the art, the skilled chemist/clinician would have to carry out undue experimentation to treat the many cardiovascular disorders claimed herein.

2. **Lack of Written Description**: Claims 13, 14, 36, 37, 43, 44, 50, 51, 60, 61, 66-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to "a method of preventing adhesion of substances to a foreign surface..." (i.e., coating an implant, catheter, or heart pacemaker). However, the specification does not appear to provide a process for how an implant, catheter, or heart pacemaker can be coated. The specification does not teach how a coating composition could be made, or what ingredients could be involved. Thus, said claims clearly lack a written description.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 3, step (a) recites the limitation of "treating a compound not of formula I...", it is unclear what is meant by the phrase "a compound not of formula I". Said phrase has indefinite metes and bounds because the structure of such a compound is indeterminate.

b. Also, claim 3, step (c) is still unclear as to which compound is converted in to which. That is, it is unclear what is meant by the phrase "one or more of R, R^1, R^2, and R^4 different than in a compound of formula I". If R, R^1, R^2, and R^4 were not as defined as for those in formula (I), then what would they be?

c. Claims 10 and 11 are rejected as being dependent on claim 3.

4. Claims 62-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims are drawn to "A intermediate compound of a compound according to claim..." However, the compound of claim 4, 22, 29, or 51 has more than one intermediates.

The final product has two intermediates, namely, formula III and formula IV. Thus, in said claims, it is unclear if the intermediate of formula III or IV is claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 22, 24-26, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by **Bhaduri et. al.** (cited in the previous action). As stated in the previous action, the disclosed compound reads on the claimed formula with the following substituents:

i. R and R_1, each represents a hydrogen atom;

ii. Z is absent, n = 1, and m = 1;

iii. Y is an alkenyl group of 2 carbon atoms;

iv. R^2 and R^3, each represents an ethyl group;

v. R^4 is an unsubstituted phenyl group.

Note, both provisos in claim 22 do not exclude the compound of Bhaduri et. al. That is, the first proviso excludes compounds having R^1 as NH_2 (an amino group on the benzo ring); however, the disclosed compound does not have NH_2 on the benzo ring. Thus, the first proviso

is not applicable to the teaching of Bhaduri et. al. The second proviso excludes compounds having R^4 as a phenylalkyl group which is not the case for the disclosed compound.

6. Claims 22, 24-27, 52, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by **Dean et. al.** (J. Het. Chem., (1982), 19(5), pp. 1117-24). Dean disclose a compound by the name, "*4 (3H)-Quinazolinone, 3-(2-aminoethyl)-2-(4-methoxyphenyl)-*", which falls within the formula I of the instant claims 22 and 51 with the following substituents:

vi. R and R_1, each represents a hydrogen atom;

vii. Z and Y are absent, n = 1, and m = 1;

viii. R^2 and R^3, each represents a hydrogen atom;

ix. R^4 is a substituted phenyl group.

7. Claims 22, 24-27, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by **Nielsen et. al.** (Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemistry, (1980), B34(9), pp. 637-42). Nielsen et. al. disclose a compound by the name, "*4(3H)-Quinazolinone, 3-[3-(dimethylamino)propyl]-2-phenyl-*", which falls within the formula I of the instant claims 22 and 51 with the following substituents:

x. R and R_1, each represents a hydrogen atom;

xi. Z and Y are absent, n = 1, and m = 2 (or vice versa);

xii. R^2 and R^3, each represents an alkyl group;

xiii. R^4 is an unsubstituted phenyl group.

8. Claims 22-27, and 52-55 are rejected under 35 U.S.C. 102(b) as being anticipated by **Zimaity et. al.** (Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal

Chemistry, (1977), 15(8), pp. 750-1). Zimaity et. al. disclose a compound by the name, "*4(3H)-Quinazolinone, 3-[(butylamino)methyl]-2-(4-methylphenyl)*", which falls within the formula I of the instant claims 22 and 51 with the following substituents:

xiv. R and R_1, each represents a hydrogen atom;

xv. Z and Y are absent, n = 1, and m = 0 ;

xvi. R^2 and R^3, each represents an alkyl group (i.e., "A" is butyl);

xvii. R^4 is a substituted phenyl group.

Again, the provisos in claims 22, 23, 52, and 53 do not exclude compounds of Dean et. al., Nielsen et. al., and Zimaity et. al.

Claim Objections

9. Claims 28, and 34 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 28 is drawn to a compound with Z as phenylene which is not taught by the above references. Claim 34 is drawn to "a method for the prophylaxis and/or therapy of a thrombotic disorder...", which is not taught by the above references either.

10. Claims 56-58 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The teachings of Dean et. al., Nielsen et. al., and Zimaity et. al. anticipate claim 51 for a compound. However, because said teachings do not relate a

pharmaceutical composition or a therapy to the disclose compound, they cannot anticipate the pharmaceutical composition and therapy recited in claims 56-58.

Allowable Subject Matter

11. Claims 1, 2, 4, 7, 9, and 15-21 are allowed because the above references do not teach a compound of quinazolinone which has a side chain containing a guanidine (i.e, -N-C(=NH)-NH_2).

12. Claims 29, 30, 40, 41, 47, 48 allowed because the above references do not teach a quinazolinone compound having a side chain with phenylene, nor do they teach a pharmaceutical composition, or therapy comprising a compound as claimed herein.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-T (~10 am ~ 8:30 pm) starting from February 22nd, 2004.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at 571-272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting SPE of 1624, at 571-272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

T. Truong
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April 12, 2004